

created doctrine of obviousness-type double patenting as being unpatentable over claims 34-58 of copending Application No. 09/257,166 in view of Gelfand et al. (U.S. Patent Application No. 5,310,652) and Birch et al. (U.S. Patent Application No. 5,677,152). This rejection is traversed.

In the presently claimed invention, a mixture is subjected in a single step to a thermocycling reaction. The claimed single mixture includes RNA, buffer, first and second primers, deoxynucleotides or derivatives, at least one terminating nucleotide and at least two thermostable DNA polymerases with differing abilities to incorporate the terminating nucleotide, at least one of the polymerases having reverse transcriptase activity. Through the use of such a mixture, transcription, amplification and sequencing can advantageously be achieved in the same step.

The "copending claims", which describe simultaneously amplification and sequencing nucleic acids using two different polymerases, do not encompass a single mixture containing the above-described components. Additionally, the copending claims nowhere teach or suggest that transcription, amplification and sequencing could be achieved in the same step, as is the case in the presently claimed invention.

As the Office Action notes Gelfand et al. disclose a one-tube, one polymerase amplification of target RNA sequences using a polymerase with reverse transcriptase activity. However, Gelfand et al. does not encompass a single mixture containing the above-described components (although, as discussed in our last Amendment, Gelfand et al. do, at Col. 6, lines 34-35, "require only one enzyme"). Additionally, Gelfand et al. nowhere teach or suggest that transcription, amplification and sequencing could be achieved in the same step, as is the case in the presently claimed invention.

Birch et al. describe use of a polymerase-inhibiting agent in nucleic acid amplifications. However, Birch et al. does not encompass a single mixture containing the above-described components. Additionally, Birch et al. nowhere teach or suggest that transcription, amplification and sequencing could be achieved in the same step, as is the case in the presently claimed invention.

The Office Action asserts that one of ordinary skill in the art would have been motivated to modify the methods of copending claims by application towards RNA using a polymerase with reverse transcriptase activity, and/or application of a polymerase-inhibiting agent.

However, Applicants respectfully submit that, even if the Examiner's above assertion were to be true, such a modification would also lead to a two step procedure of amplification/sequencing and amplification/transcription. Applicants can not find any teaching or suggestion in any of the applied references to a single mixture containing the above-described components or that transcription, amplification and sequencing could be achieved in the same step. Of course, Applicants can also not find any teaching or suggestion in any of the applied references that such a mixture would be effective to achieve transcription, amplification and sequencing in the same step, as has been shown in the present specification, particularly in view of the unpredictability from the prior art which effects will be seen when using the claimed reversibly inhibited polymerases in sequencing reactions.

Thus, Applicants respectfully submit that, even if one of ordinary skill would have been motivated to combine the "copending claims" with Gelfand et al. (which they would not have been) the presently claimed invention would not have been achieved. Thus,

Applicants respectfully submit that the presently claimed invention would not have been obvious over the combination of the "copending claims," Gelfand et al. and Birch et al.

The Office Action rejects claims 1-126, 134-137 and 143-145 under 35 U.S.C. 103(a) as being obvious over the combination of Koster et al. (U.S. Patent No. 5,928,906) in view of Gelfand et al. and Birch et al. Similarly, claims 132-133 and 141-142 are rejected under 35 U.S.C. 103(a) as being obvious over the combination of Koster et al. in view of Gelfand et al. and Birch et al. and further in view of Hill (U.S. Patent No. 5,525,492). These rejections are traversed.

As the Office Action notes, Koster et al. disclose methods "requiring two different polymerases..." As the Office Action also notes, the Koster et al. patent does not disclose DNA polymerase-mediated reverse transcription coupled to PCR amplification. However, the Office Action asserts that one of ordinary skill in the art would have been motivated to modify the method of Koster et al. by application towards RNA using a polymerase with reverse transcriptase activity because Gelfand et al. disclosed the advantages of combined reverse-transcription and amplification.

However, as discussed above for the rejection over the combination including "copending claims", Koster et al. do not encompass a single mixture containing the above-described components. Additionally, Koster et al. nowhere teach or suggest that transcription, amplification and sequencing could be achieved in the same step, as is the case in the presently claimed invention.

Additionally, as discussed above for the other rejection, Gelfand et al. does not encompass a single mixture containing the above-described components (again although, Gelfand et al. do, at Col. 6, lines 34-35, "require only one enzyme"). Additionally, Gelfand

et al. nowhere teach or suggest that transcription, amplification and sequencing could be achieved in the same step, as is the case in the presently claimed invention.

Birch et al., as discussed above, does not encompass a single mixture containing the above-described components. Additionally, Birch et al. nowhere teach or suggest that transcription, amplification and sequencing could be achieved in the same step, as is the case in the presently claimed invention.

Hill also does not encompass a single mixture containing the above-described components. Additionally, Hill nowhere teaches or suggests that transcription, amplification and sequencing could be achieved in the same step, as is the case in the presently claimed invention. Thus, Hill fails to make up for the deficiencies in the combination of Koster et al., Gelfand et al. and Birch et al.

The Office Action asserts that one of ordinary skill in the art would have been motivated to modify the methods of the Koster et al. by application towards RNA using a polymerase with reverse transcriptase activity, and/or application of a polymerase-inhibiting agent.

However, as is the case for the rejection based on the "copending claims", Applicants respectfully submit that, even if the Examiner's above assertion were to be true, such a modification would lead to a two step procedure of amplification/sequencing and amplification/transcription. Applicants can not find any teaching or suggestion in any of the applied references to a single mixture containing the above-described components or that transcription, amplification and sequencing could be achieved in the same step. Of course, Applicants can also not find any teaching or suggestion in any of the applied references that such a mixture would be effective to achieve transcription, amplification and

sequencing in the same step, as has been shown in the present specification.

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this paper is not being timely filed, the applicants respectfully petition for ~~an appropriate extension of time. Any fees for such an extension together with any~~ additional fees may be charged to Counsel's Deposit Account 01-2300.

Respectfully submitted,

Arent Fox Kintner Plotkin & Kahn



Robert K. Carpenter
Attorney for Applicants
Reg. No. 34,794

1050 Connecticut Ave. NW
Suite 600
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810

RKC:tdd

Encls: Petition for Extension of Time